## REMARKS

Election/Restriction

Applicants maintain that the restriction is improper for the reasons set forth in the response to the previous Office Action. Applicants acknowledge that the compounds of Groups I-III are classified in separate subclasses but maintain that there is no evidence on the record that searching these separate subclasses would be an undue burden since only one subclass has been identified for each Group.

Oath/Declaration

A new Oath/Declaration was submitted on October 31, 2001 which properly identifies the serial number of this application as well as the provisional application as 60/135,502. The first paragraph of the specification has been amended to correct the reference to the serial number of the provisional application.

Rejections Under 35 U.S.C. § 112, second paragraph

Applicants have amended claim 23 to recite "raf kinase" to overcome the rejection under 35 U.S.C. § 112, second paragraph. This amendment does not limit the scope of the claims.

35 U.S.C. §112, first paragraph

Applicants acknowledge that the Examiner does not have access to the decision *Ex Parte Henning* (Serial No. 08/628,250). A copy of this decision has been provided. This application has now issued as U.S. Patent No. 6,310,068, so the decision is publicly available.

Applicants also acknowledge that claims 15-25 include the treatment of diseases other than cancer and maintain the specification provides enabling disclosure for these treatment methods when considered as a whole. The application does specifically identify the treatment of tumors and/or cancer cell growth with the claimed compounds but one skilled in the art would recognize that these compounds are not limited to the treatment of such diseases based on the disclosure within the detailed description and the assays provided illustrating activity of the

compounds of Formula I. The general dosage regiments given on pages 14-17 provide sufficient guidance for one skilled in the art to administer these compounds to a host so as to inhibit raf kinase and thereby treat a disease within the host mediated by raf kinase.

Rejection Under 35 U.S.C. § 102(e)

With the identification of the proper provisional application (S.N. 60/135,502), Applicants maintain the instantly claimed compounds are entitled to a priority date of December 22, 1997.

Amended claims 1-10 and 24-25 define compounds which have an aryl/heteroaryl substituted heteroaryl group on one side of the urea functional group and a bridged aromatic group on the other side of the urea functionality urea. These claims were amended through the amendments to claims 1, 4, 5, and 7 to exclude the compound N-(3-t- butyl-1-(4-methylphenyl)pyrazol-5-yl)-N'-(2,4-dichlorolphenyl)urea disclosed by Regan et al. in the provisional application 60/064,102 (the priority document to U.S. 6,080,763). Therefore, there is no longer a basis for the rejection of these claims under 35 USC §102(e).

Rejections Under 35 U.S.C. § 103

Regan et al.

As indicated above, claims 1-10 and 24-25 now define compounds which have an aryl/heteroaryl substituted heteroaryl group on one side of the urea functional group and a bridged aromatic group on the other side of the urea functionality urea. The claimed compounds are structurally unobvious over the compound N-(3-t- butyl-1-(4-methylphenyl)pyrazol-5-yl)-N'-(2,4-dichlorolphenyl)urea disclosed by Regan et al. in the provisional application 60/064,102 on page 9. Regan et al. provides no hint or suggestion to modify this compound to incorporate a bridged aromatic group on the 2,4-dichlorophenyl ring.

Creswell et al.

As discussed above, Claims 1-5, 7-10 and 24-25 are now directed to compounds wherein

"B" of Formula I is a bridged aromatic group and "A" of formula I is a heteroaryl group substituted by an aryl/heteroaryl group ($R^2$) as well as an alkyl/cycloalkyl group ($R^1$). The disclosure of Creswell et al. is so broad as to provide no hint or suggestion of preparing such compounds. In maintaining this rejection a comparison of heteraryl group "A" to formula (8) at column 3 of Creswell is made. However, there is no suggestion or motivation to match the structure of formula (8) for "Het" of Creswell with a bridged aromatic group such as group "B" of formula I herein from the broad description of the substituents $R_1$, $R_2$ and $R_3$ on the phenyl ring in Formula I of Creswell.

As to the specific urea compounds disclosed in the Examples of Creswell, none have a bridged aromatic group consistent with "B" herein. Therefore, no direction is given when to select benzoyl or benzyl substituents for $R_1$, $R_2$ or $R_3$, which provides a bridged aromatic group. In the absence of such direction, it would not be obvious to prepare the compounds claimed herein.

New Grounds of Rejection Under 35 U.S.C. § 112, first paragraph

1) The specification has been amended to provide support for the definition of Ar in the claims as a 5-10 member aromatic structure. This amendment does not add new matter in that the "5-6 member" aromatic structures, for Ar are said to be preferred and the '5-10 member" aromatic structures for Ar were described in the original claims.

2) In rejecting claims 1-10 and 15-25 under 35 U.S.C. § 112, first paragraph, it is alleged the specification provides no disclosure on how the starting materials are obtained to prepare the claimed compounds. Applicants submit the "General Method for Substituted Aniline Synthesis" described on page 23 provides sufficient guidance for the preparation of starting materials that form group B of formula I when reacted with an aryl isocyanate. In addition, the general methods described on pages 10-13 of the specialized outline how to synthesize aryl amine starting materials by the formation of nitroaryls followed by reduction. Furthermore, the publications listed on pages 10 and 11, which are incorporated in the specification by reference, describe methods for synthesizing aryl amine starting materials. Therefore, the specification is

clearly enabling for the complete scope of compounds defined in claims 1-10 and 15-25.

New Grounds of Rejection Under 35 U.S.C. § 112, second paragraph

1) Applicants maintain that the open meaning of the term "containing" in the phrase "containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur" within definition of B is appropriate since it is used in the context of describing members of the aromatic structure, which clearly additionally includes carbon.

2) Applicants maintain it is appropriate for Claim 17 to include the 3 ring formula with the substituent $R^5$ as defined in Claim 17. This 3-ring formula is consistent with the scope of "B" defined in claim 15 in that it includes the substituents of X defined in Claim 15 ($C_1$-$C_{10}$ alkyl, alkenyl, cycloalkyl, etc.) which can appear on B, plus "hydrogen," which is consistent with B being unsubstituted. But for the substituent "hydrogen", $R^5$ is not broader than X.

3) The formula in Claim 18 has been amended to specify values for the subscript of X within the scope of "n-1". The values for the original variable "n" ranged from 0-3. With the substituent Y-$Q_1$-$Z_{n1}$ present on Q, the maximum number of "x" substituents is 2.

4) The language the examiner refers to in claim 18 (and claim 4) has been amended so that "$Q_1$" is consistent with "Ar."

5) The language the examiner refers to in claim 19 ( and amended claim 5 ) regarding "Y-Ar is phthalimidinyl" has been cancelled.

6) Claim 15 has been amended to recite a host.

Publication by Bruder et al. in combination with Regan (U.S. Patent 6,080,763)

The publication by Bruder et al. discloses that adenovirus infection activates Raf-1 and MAPK pathways and that IL-8 production is induced by adenovirus infection. Bruder et al. also discloses that the raf kinase inhibitor, forskolin, inhibited the adenovirus infection-induced MAPK activation and IL-8 production. These findings provide no indication or guidance that

1) compounds which inhibit the release of inflammatory cytokines, such as those disclosed by Regan et al., result in or may result in the inhibition of raf activity, or

2) the inflammation resulting from adenovirus infection (pathological conditions) or

chronic inflammatory disease is mediated by raf kinase. Therefore, it would be not be obvious to treat diseases mediated by raf kinase with the compounds of Regan et al. based on the teachings therein combined with the teachings of Bruder et al.

The teachings of Bruder et al. fail to provide sufficient guidance or direction to lead on skilled in the art to employ the compounds of Regan et al. in treating raf kinase mediated disease since the paper by Bruder et al. provides no link between inhibiting raf kinase activity and treating inflammatory diseases. Bruder et al. acknowledge this link has not been shown by the following statements on page 402, lines 26-28 and 57-60.

"The finding that adenovirus infection activates the raf/MAPK signal pathway raises the possibility that activation of this pathway is necessary for efficient adenovirus infection." (emphasis added) lines 26-28 and

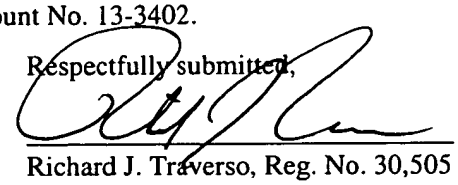
"Alternatively, it is possible that activation of this pathway is not important for efficient infection and that it is a side effect of the infection" lines 57-60.

In the absence of the definitive teachings by Bruder et al. of the role of the raf/kinase pathway in the inflammatory response, it would not obvious to one skilled in the art to use the compounds of Regan to treat diseases mediated by raf kinase. The paper shows only that the raf kinase inhibitor, forskolin, blocks the infection-induced activation of the raf kinase pathway. There is no indication that the source or the symptoms of inflammation are tracked with the raf kinase inhibitor forskolin. Furthermore, assuming that the possibility presented by Bruder et al. is confirmed, i.e., that activation of raf pathway is necessary for efficient adenovirus infection. There is no hint or suggestion the compounds of Regan would be effective to inhibit raf kinase. Bruder et al., provides no hint or suggestion that compounds which inhibit cytokine production involved in inflammation necessarily inhibit raf kinase. Therefore, the methods claimed herein which employ an amount of compounds of Formula I effective to inhibit raf kinase are not obvious in view of these combined teachings.

Based on the above remarks, Applicants submit that all pending claims are in a form suitable for allowance and patentable over the cited references. Therefore, withdrawal of the rejections and allowance of these claims are earnestly solicited.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Date: June 19, 2002

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**IN THE SPECIFICATION**:

The first paragraph on page 1 has been amended as follows:

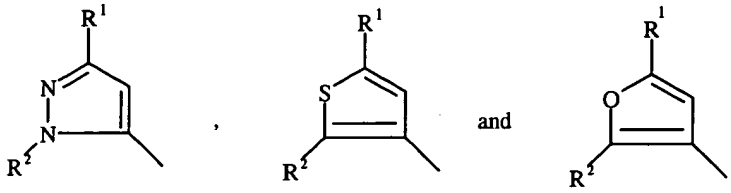
This application is a continuation of Serial No. 09/303,621 filed December 22, 1998. This application claims priority of provisional application Serial No. ~~60/126,439~~ 60/135,502 filed December 22, 1997.

**IN THE CLAIMS**:

1. (Amended) A compound of formula I or a pharmaceutically acceptable salt thereof

A-NH-C-NH-B I

wherein A is a heteroaryl selected from the group consisting of



wherein $R^1$ is selected from the group consisting of $C_3$-$C_{10}$ alkyl, $C_3$-$C_{10}$ cycloalkyl, up to per-halosubstituted $C_1$-$C_{10}$ alkyl and up to per-halosubstituted $C_3$-$C_{10}$ cycloalkyl;

B is an ~~a substituted or unsubstituted~~, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, substituted by -Y-Ar and optionally ~~wherein if B is a substituted group, it is~~ substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and $X_n$,

wherein n is ~~0-3~~ 0-2 and each X is independently selected from the group consisting of –

CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, $C_1$-$C_{10}$ alkyl, $C_2$-$C_{10}$ alkenyl, $C_1$-$C_{10}$ alkoxy, $C_3$-$C_{10}$ cycloalkyl, $C_6$-$C_{14}$ aryl, $C_7$-$C_{24}$ alkaryl, $C_3$-$C_{13}$ heteroaryl, $C_4$-$C_{23}$ alkheteroaryl, substituted $C_1$-$C_{10}$ alkyl, substituted $C_2$-$C_{10}$ alkenyl, substituted $C_1$-$C_{10}$ alkoxyl, substituted $C_3$-$C_{10}$ cycloalkyl, and substituted $C_4$-$C_{23}$ alkheteroaryl ~~and Y~~ Ar;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein $R^5$ and $R^{5'}$ are independently selected from H, $C_1$-$C_{10}$ alkyl, $C_2$-$C_{10}$ alkenyl, $C_3$-$C_{10}$ cycloalkyl, $C_6$-$C_{14}$ aryl, $C_3$-$C_{13}$ heteroaryl, $C_7$-$C_{24}$ alkaryl, $C_4$-$C_{23}$ alkheteroaryl, up to per-halosubstituted $C_1$-$C_{10}$ alkyl, up to perhalosubstituted $C_2$-$C_{10}$ alkenyl, up to per-halosubstituted $C_3$-$C_{10}$ cycloalkyl, up to per-halosubstituted $C_6$-$C_{14}$ aryl and up to per-halosubstituted $C_3$-$C_{13}$ heteroaryl,

wherein Y is -O-, -S-, $-N(R^5)-$, $-(CH_2)_m-$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-NR^5C(O)NR^5R^{5'}-$, $-NR^5C(O)-$, $-C(O)NR^5-$, $-O(CH_2)_m-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$,

m = 1-3, and $X^a$ is halogen; and

Ar is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by $Z_{n1}$, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-C(O)R^5$, $NR^5C(O)R^{5'}$, $C_1$-$C_{10}$ alkyl, $C_3$-$C_{10}$ cycloalkyl, $C_6$-$C_{14}$ aryl, $C_3$-$C_{13}$ heteroaryl, $C_7$-$C_{24}$ alkaryl, $C_4$-$C_{23}$ alkheteroaryl, substituted $C_1$-$C_{10}$ alkyl, substituted $C_3$-$C_{10}$ cycloalkyl, substituted $C_7$-$C_{24}$ alkaryl and substituted $C_4$-$C_{23}$ alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$, and

wherein $R^2$ is $C_6$-$C_{14}$ aryl, $C_3$-$C_{14}$ heteroaryl, substituted $C_6$-$C_{14}$ aryl or substituted $C_3$-$C_{14}$ heteroaryl,

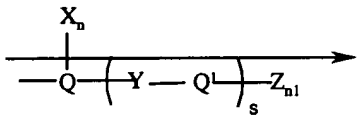
wherein if $R^2$ is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and $V_n$,

wherein n = 0-3 and each V is independently selected from the group consisting of -CN, -$CO_2R^5$, -$C(O)NR^5R^{5'}$, -$OR^5$, -$SR^5$, -$NR^5R^{5'}$, -$C(O)R^5$, -$OC(O)NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$SO_2R^5$, -$SOR^5$, -$NR^5C(O)R^{5'}$, -$NO_2$, $C_1$-$C_{10}$ alkyl, $C_3$-$C_{10}$ cycloalkyl, $C_6$-$C_{14}$ aryl, $C_3$-$C_{13}$ heteroaryl, $C_7$-$C_{24}$ alkaryl, $C_4$-$C_{24}$ alkheteroaryl, substituted $C_1$-$C_{10}$ alkyl, substituted $C_3$-$C_{10}$ cycloalkyl, substituted $C_6$-$C_{14}$ aryl, substituted $C_3$-$C_{13}$ heteroaryl, substituted $C_7$-$C_{24}$ alkaryl and substituted $C_4$-$C_{24}$ alkheteroaryl,

where if V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, -$CO_2R^5$, -$C(O)R^5$, -$C(O)NR^5R^5$, -$NR^5R^{5'}$, -$OR^5$, -$SR^5$, -$NR^5C(O)R^{5'}$, -$NR^5C(O)OR^{5'}$ and -$NO_2$;

wherein $R^5$ and $R^{5'}$ are each independently as defined above.

**4.** (Amended) A compound of claim 1, ~~wherein B is~~




wherein

Y is selected from the group consisting of –O-, -S-, -$CH_2$-, -$SCH_2$-, -$CH_2S$-, -CH(OH)-, -C(O)-, -$CX^a_2$, -$CX^aH$-, -$CH_2O$- and -$OCH_2$- , and

$X^a$ is halogen~~,~~

~~Q is a six-member aromatic structure containing 0-2 nitrogen, unsubstituted or substituted by halogen, up to per-halosubstitution;~~

~~$Q^1$ is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or substituted by halogen up to per-halosubstitution,~~

~~X, Z, n and n1 are as defined in claim 1, and s = 0 or 1~~.

5. (Amended) A compound of claim 4, wherein

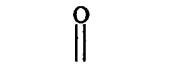
~~Q is phenyl or pyridinyl, unsubstituted or substituted by halogen, up to per-halosubstitution,~~

~~Q~~$^1$ Ar is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, unsubstituted or substituted by halogen, up to per-halo substitution, ~~or Y-Q$^1$ is phthalimidinyl unsubstituted or substituted by halogen up to per-halo substitution~~, and

Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein $R^6$ is hydrogen, $C_1$-$C_{10}$-alkyl or $C_3$-$C_{10}$-cycloalkyl and $R^7$ is selected from the group consisting of hydrogen, $C_3$-$C_{10}$-alkyl, $C_3$-$C_6$-cycloalkyl and $C_6$-$C_{10}$-aryl, wherein $R^6$ and $R^7$ can be substituted by halogen or up to per-halosubstitution.

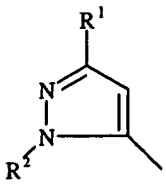
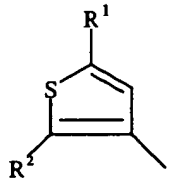
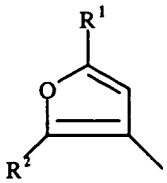
7. (Amended) A compound of claim 4, wherein Ar ~~Q is phenyl, Q~~$^1$ is phenyl or pyridinyl, Y is –O-, -S- or $-CH_2-$, and X and Z are independently Cl, F, $NO_2$ or $CF_3$.

15. (Amended) A method for the treatment of disease mediated by raf kinase, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a host in need thereof:



A-NH-C-NH-B I

wherein A is a heteroaryl selected from the group consisting of



and


wherein $R^1$ is selected from the group consisting of $C_3$-$C_{10}$ alkyl, $C_3$-$C_{10}$ cycloalkyl, up to per-halosubstituted $C_1$-$C_{10}$ alkyl and up to per-halosubstituted $C_3$-$C_{10}$ cycloalkyl;

B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and $X_n$,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, $CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, $C_1$-$C_{10}$ alkyl, $C_{2-10}$-alkenyl, $C_{1-10}$-alkoxy, $C_3$-$C_{10}$ cycloalkyl, $C_6$-$C_{14}$ aryl, $C_7$-$C_{24}$ alkaryl, $C_3$-$C_{13}$ heteroaryl, $C_4$-$C_{23}$ alkheteroaryl, substituted $C_1$-$C_{10}$ alkyl, substituted $C_{2-10}$-alkenyl, substituted $C_{1-10}$-alkoxy, substituted $C_3$-$C_{10}$ cycloalkyl, substituted $C_4$-$C_{23}$ alkheteroaryl and -Y-Ar;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein $R^5$ and $R^{5'}$ are independently selected from H, $C_1$-$C_{10}$ alkyl, $C_{2-10}$-alkenyl, $C_3$-$C_{10}$ cycloalkyl, $C_6$-$C_{14}$ aryl, $C_3$-$C_{13}$ heteroaryl, $C_7$-$C_{24}$ alkaryl, $C_4$-$C_{23}$ alkheteroaryl, up to per-halosubstituted $C_1$-$C_{10}$ alkyl, up to per-halosubstituted $C_{2-10}$-alkenyl , up to per-halosubstituted $C_3$-$C_{10}$ cycloalkyl, up to per-halosubstituted $C_6$-$C_{14}$ aryl and up to per-halosubstituted $C_3$-$C_{13}$ heteroaryl, wherein Y is - O-, -S-, $-N(R^5)$-, $-(CH_2)_m$-, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$-, $-CX^a_2$-, $-S-(CH_2)_m$- and $-N(R^5)(CH_2)_m$-,

m = 1-3, and $X^a$ is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by $Z_{n1}$, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-C(O)R^5$,

$-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, $C_1$-$C_{10}$ alkyl, $C_3$-$C_{10}$ cycloalkyl, $C_6$-$C_{14}$ aryl, $C_3$-$C_{13}$ heteroaryl, $C_7$-$C_{24}$ alkaryl, $C_4$-$C_{23}$ alkheteroaryl, substituted $C_1$-$C_{10}$ alkyl, substituted $C_3$-$C_{10}$ cycloalkyl, substituted $C_7$-$C_{24}$ alkaryl and substituted $C_4$-$C_{23}$ alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$ , $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$, and

wherein $R^2$ is $C_6$-$C_{14}$ aryl, $C_3$-$C_{14}$ heteroaryl, substituted $C_6$-$C_{14}$ aryl or substituted $C_3$-$C_{14}$ heteroaryl,

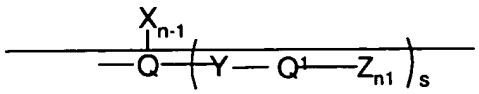
wherein if $R^2$ is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and $V_n$,

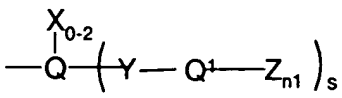
wherein n = 0-3 and each V is independently selected from the group consisting of -CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-OC(O)NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)OR^{5'}$, $-SO_2R^5$, $-SOR^5$, $-NR^5C(O)R^{5'}$, $-NO_2$, $C_1$-$C_{10}$ alkyl, $C_3$-$C_{10}$ cycloalkyl, $C_6$-$C_{14}$ aryl, $C_3$-$C_{13}$ heteroaryl, $C_7$-$C_{24}$ alkaryl, $C_4$-$C_{24}$ alkheteroaryl, substituted $C_1$-$C_{10}$ alkyl, substituted $C_3$-$C_{10}$ cycloalkyl, substituted $C_6$-$C_{14}$ aryl, substituted $C_3$-$C_{13}$ heteroaryl, substituted $C_7$-$C_{24}$ alkaryl and substituted $C_4$-$C_{24}$ alkheteroaryl,

where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^5$, $-NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and $-NO_2$,

wherein $R^5$ and $R^{5'}$ are each independently as defined above.

**18.** (Amended) A method of claim 15, wherein B is





wherein

Y is selected from the group consisting of –O-, -S-, $-CH_2-$, $-SCH_2-$, $-CH_2S-$, -CH(OH)-, -C(O)-, $-CX^a_2$, $-CX^aH-$, $-CH_2O-$ and $-OCH_2-$,

$X^a$ is halogen,

Q is a six member aromatic structure containing 0–2 nitrogen, unsubstituted or substituted by halogen, up to per-halosubstitution;

$Q^1$ is a mono- or bicyclic aromatic structure of 5-10 members with 3 to 10 carbon atoms and ~~0-4~~ 0-2 members of the group consisting of N, O and S, unsubstituted or substituted by halogen up to per-halosubstitution,

X, Z, ~~n~~ and n1 are as defined in claim 15, and s = 0 or 1.

**19.** (Amended) A method as in claim 18, wherein

Q is phenyl or pyridinyl, unsubstituted or substituted by halogen, up to per-halosubstitution,

$Q^1$ is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, ~~or Y-$Q^1$ is phthalimidinyl substituted or unsubstituted by halogen up to per-halo substitution,~~ and

Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein $R^6$ is hydrogen, $C_1$-$C_{10}$-alkyl or $C_3$-$C_{10}$-cycloalkyl and $R^7$ is selected from the group consisting of hydrogen, $C_3$-$C_{10}$-alkyl, $C_3$-$C_6$-cycloalkyl and $C_6$-$C_{10}$-aryl, wherein $R^6$ and $R^7$ can be substituted by halogen or up to per-halosubstitution.

23. (Amended) A method as in claim 15, comprising administering an amount of compound of formula I effective to inhibit raf kinase.

EXHIBIT

JUN - 1 2001

The opinion in support of the decision being entered today was not written for publication and is not precedent of the Board.

MERCK-1773

Paper No. 17

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte HENNING BÖTTCHER, KARL J BUHRING, HARTMUT GREINER, GERD BARTOSZYK, and CHRISTOPH SEYFRIED,

MAILED

MAY 29 2001

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

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Appeal No. 1998-1487
Application No. 08/628,250

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ON BRIEF

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Before WINTERS, WILLIAM F. SMITH and MILLS, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 13-29, which are all of the claims pending in this application.

We reverse.

STATUS RE: NOT. OF ALLOWANCE
11/29/01



DATED 6/1/01

Claims 13 and 16 are illustrative of the claims on appeal and read as follows:

13. The compound 3-[4-(4-(4-cyanophenyl)-1-piperazinyl)butyl]-5-cyanoindole hydrochloride.

16. A method comprising administering to a patient an anxiolytic, antidepressant, antipsychotic, neuroleptic or antihypertensive active effective amount of the compound of claim 13 for the treatment or control of an illness associated with such activity.

The prior art references relied upon by the examiner are:

| | | |
|---|---|---|
| Böttcher et al. (Böttcher 1) | 5,418,237 | May 23, 1995 |
| German Patent Application Böttcher et al. (Böttcher 2) | 41 01 686 A1 | Jul. 23, 1992 |

Grounds of Rejection

Claims 16, 20, 25 and 29 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to enable one of skill in the art to make and use the invention.

Claims 16, 20, 25 and 29 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellants regard as the invention.

Claims 13-29 stand rejected under 35 U.S.C. § 103 as unpatentable for obviousness over Böttcher 1 or 2.

## DISCUSSION

In reaching our decision in this appeal, we have given consideration to the appellants' specification and claims, to the applied prior art references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the noted rejections, we make reference to the examiner's Answer for the examiner's reasoning in support of the rejection, and to the appellants' Brief for the appellants' arguments thereagainst. As a consequence of our review, we make the determinations which follow.

### 35 U.S.C. § 112, first and second paragraphs

Claims 16, 20, 25 and 29 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to enable one of skill in the art to make and use the invention. Claims 16, 20, 25 and 29 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellants regard as the invention.

The second paragraph of 35 U.S.C. § 112 requires claims to set out and circumscribe a particular area with a reasonable degree of precision and particularity. In re Johnson, 558 F.2d 1008, 1015, 194 USPQ 187, 193 (CCPA 1977). In making this

determination, the definiteness of the language employed in the claims must be analyzed, not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. Id.

The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. § 112, second paragraph, is whether the claims meet the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. As stated above, if the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. See Ex parte Porter, 25 USPQ2d 1144, 1146 (Bd. Pat. App. & Int. 1992). With this as background, we analyze the specific rejections under 35 U.S.C. § 112, second paragraph, made by the examiner of the claims on appeal.

With respect to both rejections under 35 U.S.C. § 112, the examiner is troubled by the language "for the treatment or control of an illness associated with such activity" in claim 16 and related claims. The examiner suggests that this phrase "implies more than anxiety, depression, etc." Answer, page 4. In our view, the examiner has not applied the appropriate legal standard to the rejections for indefiniteness and lack of enablement. With regard to the rejection for claim indefiniteness, we find that claim 16, for example, clearly describes the desired activity of the claimed compound, i.e., anxiolytic, antidepressant, antipsychotic, neuroleptic or antihypertensive activities. Thus

the phrase "treatment or control of an illness associated with such activity", in claim 16 is limited by the specific activities previously recited in the claim. We find no ambiguity or indefiniteness here. The examiner appears to have confused the definiteness requirement of 35 U.S.C. § 112, second paragraph, with the enablement requirement of 35 U.S.C. § 112, first paragraph. As set forth in In re Skoll, 523 F.2d 1392, 1395, 187 USPQ 481, 482-83 (CCPA 1975), the use of a broad term in a claim does not make that claim indefinite.

With respect to the 35 U.S.C. § 112, first paragraph rejection, we find the rejection not entirely clear as to whether it is predicated on the written description or enablement requirement of 35 U.S.C. § 112, first paragraph. To the extent that the rejection is predicated upon the written description requirement, we summarily reverse as we find the examiner has failed to specifically indicate what language in the claims is inadequately supported by the original specification.

To the extent that the rejection is based on the enablement requirement of 35 U.S.C. § 112, first paragraph, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir.1997) (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Conversely, the first paragraph of

Section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification.

In addition, analysis of whether the claims under appeal are supported by an enabling disclosure requires a determination of whether that disclosure contains sufficient information regarding the subject matter of the appealed claims as to enable one skilled in the pertinent art to make and use the claimed invention. In order to establish a prima facie case of lack of enablement, the examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Morehouse, 545 F.2d 162, 165, 192 USPQ 29 32 (CCPA 1976). The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement.

The examiner suggests (Answer, page 5) that

> To the extent any illness associated with anxiety, depression ... hypertension is embraced by the claim language (e.g., A person diagnosed with cancer or AIDS may be depressed) there is no enabling disclosure for all such diseases of varying etiology. Also [the] scope of antipsychotic disorders (even if such only intended by the claim language "associated with") embraces a variety of dysfunctions such as Tourette's Syndrome, Huntington's Disease) not shown to be ... associated with simply being [a] serotonin antagonist or having dopamine activity as described in the specification, p. 2.

In our view, the specification discloses the scope of the invention in a manner discernable by one of ordinary skill in the art. We find the examiner's concerns that any illness associated with anxiety, depression, and hypertension is embraced by the claim language, and that there is no disclosure for treatment of all of such diseases of varying etiology, including AIDS, to be misplaced. For example, the specification discloses that the claimed compounds show "actions on the central nervous system, especially 5-$HT_{1A}$-antagonist and 5-HT-reuptake-inhibiting actions. They inhibit the binding of tritiated serotonin ligands to hippocampal receptors." Specification, page 2. The specification also discloses that the compounds have anxiolytic, antidepressant, antipsychotic, neuroleptic or antihypertensive activities. Id.

The examiner has not provided evidence or argument establishing that one of ordinary skill in the art with a disclosure in the specification of the above symptomology and with knowledge of the manner in which the claimed compounds are disclosed to act upon the central nervous system, would not have a sufficient teaching to treat associated anxiolytic, antidepressant, antipsychotic, neuroleptic or antihypertensive conditions.

A legal standard which governs determination of enablement under this section of the statute that does not appear to have been taken into account by the examiner is that the specification need not disclose what is well known in the art. See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94

(Fed. Cir. 1986). It is well established that enablement issues must be decided on the basis of the information imparted by appellants in the specification of the patent application under review in conjunction with the relevant prior art. Viewing a given patent specification in a vacuum apart from the prior art to determine whether the claims of such a patent application are enabled is incorrect. See, e.g., Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), ("A specification need not disclose what is well known in the art.")

From a review of Böttcher 1, it would appear that those of ordinary skill in the art are aware of how similar compounds act on the central nervous system and are aware that similar compounds possess anxiolytic, antidepressant, antipsychotic, neuroleptic or antihypertensive activities. Böttcher 1, columns 1-2.

The examiner also appears to have misapprehened what the claims actually require. The examiner (Answer, page 5) appears to set up a straw man argument suggesting that, to the extent that any illness associated with anxiety, depression or hypertension is embraced by the claim language, such as depression associated with cancer or AIDs, there is no enabling disclosure for treatment of such illnesses. However, the claims are not so broad, as they are limited to a method comprising administering to a patient an anxiolytic, antidepressant, antipsychotic, neuroleptic or antihypertensive active effective amount of the compound of claim 13 for the treatment or control of an illness associated with the specific activities recited in the claim.

For these reasons, the rejection of the claims under 35 U.S.C. § 112, first and second paragraphs are reversed.

35 U.S.C. § 103

Claims 13-29 stand rejected under 35 U.S.C. § 103 as unpatentable for obviousness over Böttcher 1 or 2.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). With this as background, we analyze the prior art applied by the examiner in the rejection of the claims on appeal.

The cited German Patent (Böttcher 2) is the equivalent of the U.S. Patent (Böttcher 1). Böttcher 1 is relied on by the examiner, and indicated to establish "compounds within the instant scope for the same uses as claimed herein, anxiety, depression, as psychotic agents, hypertension among others." Answer, page 6. The claimed compounds are indicated to "differ from the closest Böttcher 1 compound (see col. 14, lines 17-19) in two respects - 1) having a 4-cyanophenyl vs 2-cyanophenyl and

2) being the HCl salt vs. the free form." Id. Thus, the claimed compounds and the Böttcher 1 reference compounds would appear to be positional isomers.

Although the appellants would suggest that a prima facie case of obviousness has not been established by the examiner citing In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) and In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994), we find it unnecessary to determine whether or not a prima facie case of obviousness has been established by the examiner, as we find the evidence provided by appellant would outweigh any prima facie case, if established.

Appellants have provided a Declaration under 37 CFR § 1.132 of Christoph A. Seyfried as evidence of the nonobviousness of the claimed invention. The Seyfried Declaration compares the claimed (claim 13) 4-cyanophenyl compound (Compound A of the Declaration) with the 2-cyanophenyl (Compound C3 of the Declaration) of Böttcher 1. The evidence presented in the Declaration shows that compound A shows no $\alpha_1$ antagonistic action, in contrast to compound C3 which possesses $\alpha_1$ antagonistic action (Declaration pages 3 and 4 and Table II). In addition, in contrast to the prior art compound C3, compound A shows no antidopaminergic effect, which the Declarant finds to be unexpected. The antidopaminergic effect is also supported by in vivo test results. Declaration, page 4.

The Declarant summarizes (Declaration, page 4) that

> [l]ack of affinity to the $\alpha_1$ receptor and lack of anti-dopaminergic effect are important features in the profile of compounds for treating depression. Due to the lack of affinity to the $\alpha_1$ receptor cardiovascular, e.g.[,] hypotensive and/or negative inotropic side effects are not expected for A. Likewise, secondary effects such as extrapyrimidal motor effects should not occur.

In response to the Declaration evidence presented by appellants, the examiner finds that the properties relied on in showing evidence of nonobviousness, lack of $\alpha_1$ antagonistic activity and the lack of anti-dopaminergic blocking, were never expressly described in the specification, citing In re Davies, 475 F.2d 667, 670, 177 USPQ 381, 381 (CCPA 1973) and In re Zenitz, 333 F.2d 924, 928, 142 USPQ 158, 161 (CCPA 1964) and thus cannot be relied upon to support patentability.

We agree with appellants that the properties described by appellants in the Seyfried Declaration would "inherently flow" from the subject matter disclosed and described in the original application. In re Khelghatian, 364 F.2d 870, 150 USPQ 661, 666 (CCPA 1966). Compare, In re Chu, 66 F.3d 292, 298, 36 USPQ2d 1089, 1095 (Fed. Cir. 1995) ["We have found no cases supporting the position that a patent applicant's evidence and/or arguments traversing a § 103 rejection must be contained within the specification".] The specification describes that the compounds can be used as pharmacologically active substances, in particular, as anxiolytics, antidepressants, antipsychotics, neuroleptics and/or antihypertensives. Specification, page 2. Thus, the

lack of affinity to the $\alpha_1$ receptor and lack of anti-dopaminergic effect are important features in the profile of compounds for treating depression and inherently flow from their described use in the specification as antidepressants.

After evidence or arguments are submitted by the appellants in response to rejection based on obviousness, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of the argument. On balance, we believe that the totality of the evidence presented by the examiner and appellants weighs in favor of finding the claimed invention nonobvious in view of the cited references. The rejection of the claims for obviousness of the claimed invention is reversed.

## CONCLUSION

The rejections of claims 16, 20, 25 and 29 under 35 U.S.C. § 112, first and second paragraphs, and of claims 13-29 under 35 U.S.C. § 103 are reversed.

## REVERSED

SHERMAN D. WINTERS
Administrative Patent Judge

WILLIAM F. SMITH
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

) BOARD OF PATENT
) APPEALS AND
) INTERFERENCES

Appeal No. 1998-1487
Application No. 08/628,250

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